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Jere Williams Lord
1864–1933

Jere Williams Lord, dermatologist of national reputation, died on April 23rd, 1933, after a long and painful illness which he bore with consummate courage and marvelous good humor.

He was born in 1864 in Portland, Maine, where he received his early education. He moved to Baltimore in 1878. Two years later he entered the Johns Hopkins University, obtaining the degree of Bachelor of Arts in 1884. In the fall of the same year, he was admitted to the Medical School of the University of Pennsylvania and took his medical degree in 1887. The following year, while serving as Resident Physician at the Presbyterian Hospital in Philadelphia, he became acquainted with the well known dermatologist, Dr. Robert Morison, and the friendship marked the beginning of Dr. Lord's interest in the study of diseases of the skin. When the Johns Hopkins Hospital opened in 1889, Dr. Lord became associated with its Dermatological Department, was later appointed Clinical Professor of Dermatology and retained this position until sickness compelled his resignation in 1929. In the first few years of the Johns Hopkins Medical School he also found time to act as Instructor in Anatomy. From 1897 to 1902 he was Secretary of the Medical and Chirurgical Faculty of Maryland.

In June, 1898 he married Miss Evelyn Pope, a graduate of the first class of the Johns Hopkins Hospital Training School for Nurses. The older of their two sons, Llewellyn W. Lord continues to practice in his father's chosen field, while the younger, Jere W. Lord, Jr., will shortly begin his medical career.

In his younger days one of Dr. Lord's diversions was bicycling. Some of his old friends still point with pride, mingled with amusement, to the fact that at one time he was Champion of Maryland on the old high wheel!

In the later years of his life Dr. Lord's hobby was amateur farming to which he devoted himself with zest until his health began to fail.

With the passing of Jere Williams Lord an early chapter of the Johns Hopkins Dermatological Clinic comes to a close.

L. P. H.

BLOOD OF NORMAL MEN AND WOMEN

Erythrocyte Counts, Hemoglobin and Volume of Packed Red Cells of 229 Individuals

M. M. WINTROBE, M.D.

With the Technical Assistance of J. Walter Landsberg, Ph.G.

From the Department of Medicine, The Johns Hopkins University, Baltimore, Maryland

Submitted for publication June 10, 1933

In the past few years attention has been drawn to the fact that, for an examination so fundamental to clinical medicine as the blood count, little information has been available upon which to base an accurate conception of the normal. Recently a few reports on this subject have appeared but, among these, there has been some variation in the mean normal values for red cell count as well as for hemoglobin and volume of packed red cells.

It is with the object of supplying further data for the establishment of normal blood values, as well as in order to discuss the possibility that geographic differences in normal values may occur (7), that the following blood examinations, undertaken primarily for another purpose, are here presented.

MATERIAL

The material consists of three groups of subjects:

I. Eighty-six white male medical students (fig. 1). The great majority were first year students who had received a complete physical examination a few weeks prior to the blood examination. Only those definitely normal as judged by history and physical examination are included in this series. A few of the students were members of the third year class. These had not received a complete physical examination as recently as the others but could be considered in good health.

II. One hundred and one white females, chiefly nurses (fig. 1). A few female medical students are included in this group. All had recently been examined and found in good health.

III. A miscellaneous group of 42 individuals (table III). This group comprises members of both sexes, of all ages, and of the white and black races. The majority are patients who presented themselves

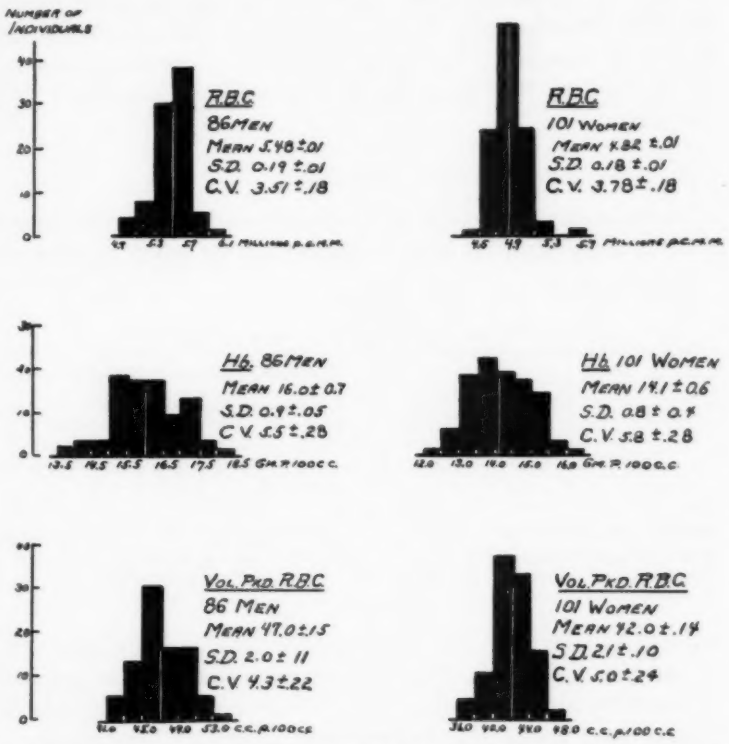

FIG. 1. FREQUENCY DISTRIBUTION OF RED CELL COUNTS, HEMOGLOBIN AND VOLUME OF PACKED RED CELLS IN 86 MEN AND 101 WOMEN

S.D. = standard deviation, C.V. = coefficient of variation. The position of the mean is indicated by the white line.

in the dispensary and who were found, on physical examination, to be normal. Nevertheless, since most of these individuals had some complaint, this group must be considered as less certainly consisting of normal individuals than groups I and II.

METHODS

The methods are the same as those employed in an earlier investigation (14, 15) and need not be again described in detail. In each instance, 5 c.c. of venous blood, collected in 10 mg. potassium oxalate was used. The counting chambers and pipettes were certified by the Bureau of Standards; the hemoglobinometer (Newcomer) was restandardized by the Van Slyke method; a special hematocrit (18) was used.

RESULTS

The frequency distribution as well as other statistical data for groups I and II are presented in figure 1 and the data for group III are summarized in table III. There is relatively little variation about the means (fig. 1) and the observed and calculated ($\pm 3 \times$ standard deviation) minima and maxima (table I) are essentially in agreement so that these groups may be considered reasonably homogenous.

TABLE I

Observed and calculated minima and maxima

	MEN (GROUP I)				WOMEN (GROUP II)			
	Minimum		Maximum		Minimum		Maximum	
	Observed	Calculated	Observed	Calculated	Observed	Calculated	Observed	Calculated
Red cell count, millions per c.mm.	4.90	4.91	5.98	6.05	4.44	4.29	5.60	5.35
Hemoglobin, grams per 100 cc	13.9	13.4	18.4	18.7	12.0	11.7	16.2	16.6
Volume packed red cells, cc. per 100 cc	41.5	40.9	54.0	53.1	36.6	35.7	48.0	48.3

THE BLOOD OF NORMAL INDIVIDUALS IN VARIOUS LOCALITIES

The members of groups I and II have come to Baltimore from all parts of the United States. Since the majority at the time of the blood examination had only recently arrived, it was thought of interest to analyze the blood values in accordance with the place of residence of the subject. The few third year medical students in group I have all been considered residents of the Eastern United States.

In Table II, in which the results of this analysis are shown, the seaboard states from Maryland northwards, as well as Pennsylvania and Vermont, are classed as "East"; Virginia, West Virginia, Kentucky, Arkansas and Louisiana, as well as the states south and east of these, are classed as "South"; the group bounded by Ohio, Indiana, Missouri,

TABLE II

Mean values for different localities

LOCALITY	MEN				WOMEN			
	Number of subjects	RBC	Hemoglobin*	Volume packed RBC†	Number of subjects	RBC	Hemoglobin*	Volume packed RBC†
		millions per c.mm.	*grams per 100 cc.*	*cc. per 100 cc.*		*millions per c.mm.*	*grams per 100 cc.*	*cc. per 100 cc.*
U. S. A. East (Groups I and II).....	61	5.40	15.8	46.6	73	4.78	14.0	41.5
U. S. A. Mid-West (Groups I and II)..	7	5.50	16.1	47.0	15	4.89	14.3	43.1
U. S. A. West (Groups I and II).....	2	5.56	16.0	48.2	2	4.70	14.1	41.5
U. S. A. South (Groups I and II)....	16	5.40	15.6	45.7	11	4.85	14.1	43.0
U. S. A. East (Emerson (3)).....	171	5.44	15.1					
U. S. A. Mid-West (Haden (7)).....	70	4.95	15.3		30	4.38	13.4	
U. S. A. Mid-West (Haden (6)).....	40	4.97	15.5	45.8	12	4.26	13.3	39.0
U. S. A. West (Osgood (11)).....	137	5.39	15.8	46.4	100	4.80	13.7	42.4
U. S. A. South (Wintrobe (14, 15)) ...	100	5.85	17.0	49.6	50	4.93	13.8	41.5
Various parts of the world (16).....	310±	5.50	16.2	46.0	210±	4.78	13.9	41.0
U. S. A. South (Foster and Johnson (4)).....	40	5.26	15.7	46.7				
Denmark (Gram and Norgäard (5))...	10	5.45	15.0	46.3	10	4.65	13.0	40.5
Denmark (Bie and Möller (1)).....	10	5.53	14.8	46.4	10	4.74	13.3	38.7
Germany (Horneffer (9)).....	40	4.96	16.0					
England, London (Price-Jones (12))..	100	5.43	14.9		100	5.01	13.9	
Average for entire series.....	477±	5.43	15.9	47.7	369±	4.85	13.9	41.8

* Corrected to correspond to values obtained by Van Slyke method.

† Corrected to correspond to volume of packed red cells in heparinized blood.

Oklahoma, Kansas, Nebraska and the Dakotas as "Mid-West"; and the states bounded on the east by Montana, Wyoming, Colorado and Texas, as "West." Although our own observations on individuals from the Mid-West are too few to be significant, Haden, and Osgood have reported blood examinations on a number of individuals from these localities, thus making some comparison possible.

Examination of the mean values for the various regions of the United States and Europe shows them to be, on the whole, in close agreement. These values correspond remarkably to the means for several hundred accurate blood determinations carried out in different parts of the world which were reviewed in 1930 (16). In so far as the observations recorded may be used as a criterion, there is certainly nothing to suggest, as Haden has intimated (7), that a wide geographic variation in blood counts occurs. The blood examinations we have made in the East agree closely with those reported in Baltimore by Emerson in 1907 (3) and are similar to values reported from Oregon (11) and from Denmark (1, 5). The values in group II for women from the South are also in close agreement with those reported by me in Louisiana (15). The values in group I for men from the South are lower than those reported by Wintrobe and Miller for men in Louisiana (14), but they are higher than the values recently recorded for that locality on a similar population by Foster and Johnson (4). The reason for these differences is not apparent, but since the average of the two last mentioned series of blood examinations is almost identical with that for men from the South reported in this communication, the differences are probably not significant from the geographic standpoint.

Indeed only the values reported by Haden (6, 7) and by Horneffer (9) are to any extent in disagreement with the other values recorded in various parts of the United States and Europe. Both of these investigators found erythrocyte counts which were lower than those reported by other observers, although their values for hemoglobin, and Haden's values for volume of packed red cells, are about the same as have been found elsewhere. Price-Jones (12) found values for hemoglobin in men somewhat lower than those reported in this country, although his red cell counts in men, as well as all his observations in women, are in exact agreement. Contradictory to Price-Jones' suggestion, Jenkins and Don (10) could find no difference between the English and American means for hemoglobin.

Examined as a whole, the values for red cell counts, hemoglobin and volume of packed red cells which have been reported from different localities in the United States and Europe, do not impress one with their variation but, in fact, one is struck by their essential similarity. There seems, therefore, to be no adequate reason why the mean of the

large series of accurate blood determinations which has now been reported, cannot be employed as the normal for healthy men and women in North America.

THE BLOOD OF ADULTS AT VARIOUS AGES

Normal blood values are now available for a large series of men and women 18 to 30 years of age, but relatively few determinations have been reported for individuals older than this. What reports there are do not show significant differences. The observations summarized in an earlier review (16) showed erythrocyte counts, hemoglobin and

TABLE III

Mean values for 42 men and women

(Group III—miscellaneous group)

NUMBER OF SUBJECTS	SEX	AGE		RACE	R.B.C.	HEMOGLOBIN	VOLUMES PACKED R.B.C.
		Range	Average				
					millions per c.mm.	*grams per 100 cc.*	*cc. per 100 cc.*
5	M	16–29	24.0	W	5.33	15.3	45.7
11	M	35–74	53.5	W	5.27	15.1	44.3
6	M	24–59	40.8	B	5.52	15.2	45.7
5	F	17–27	23.2	W	4.66	13.8	40.8
15	F	32–68	43.5	W	4.82	14.1	41.6

volume of packed red cells in men of 30 to 60 years and in men over 60 years of age to be approximately the same as those of younger men. The same was true of women except that the hemoglobin of those over 30 years of age was higher than that of younger women. It was pointed out, however, that this difference could be accounted for by differences in technique.

The purpose of table III is to compare the blood values of men and women of different age groups. As already mentioned, the individuals included in group III are not as ideal subjects for the determination of normal blood values as are those included in groups I and II, but since group III forms a fairly homogeneous series, it is of some service in comparing the blood of adult men and women of different ages.

The observations recorded in table III further corroborate the impression that no significant differences occur in normal adults as age

advances, as long as the health remains good. There is as yet no confirmation of the statement sometimes made that, after the climacteric, blood values in the two sexes become the same.

It was previously (16) stated that no adequate data regarding *racial* variation in the blood constituents here considered are available. Since that time no further data have been added. It is of interest that the blood values for 6 healthy American negroes, recorded in table III, are essentially the same as those for white persons.

THE BLOOD OF NORMAL MEN AND WOMEN

In the light of these considerations, it seems justifiable to calculate the mean values for red cell count, hemoglobin and volume of packed red cells for men and for women, as now available from a large number of accurate blood examinations, and to employ these values as the normal standard. Adding to the series previously reviewed (16) the values reported by Foster and Johnson (4) and by Price-Jones (12) as well as those for groups I and II here reported, the following mean values are found:

	Men	*Women*
Mean red cell count, millions per c.mm.....	5.40 (544)*	4.85 (387)
Mean hemoglobin, grams per 100 cc.....	16.0 (583)	13.9 (433)
Amount of hemoglobin equivalent to 5 million red cells, grams per 100 cc.....	14.8	14.3
Mean volume of packed red cells, cc. per 100 cc..	46.3 (381)	41.4 (313)

* Figures in parenthesis indicate number of subjects.

Since there is a wide inter-individual variation in the blood counts of normal individuals, it would be valuable to have accurate information concerning the limits of normal variation and to know at what point anemia, or polycythemia, may be considered present. This information is not as easily obtained as at first would seem. In any large series of blood examinations, unnoticed technical errors and errors in sampling—the inclusion of individuals who are not entirely normal—unavoidably occur. Whereas such errors tend to balance one another and consequently mean values are reasonably accurate, the lowest and highest blood values in the series cannot be accepted as accurate indices of the range of normal.

A somewhat more accurate criterion of variation is the standard

deviation, although this is also imperfect as long as some of the observations on which it is based are incorrect. In an attempt to arrive at some conclusion concerning the range of normal values for red cell

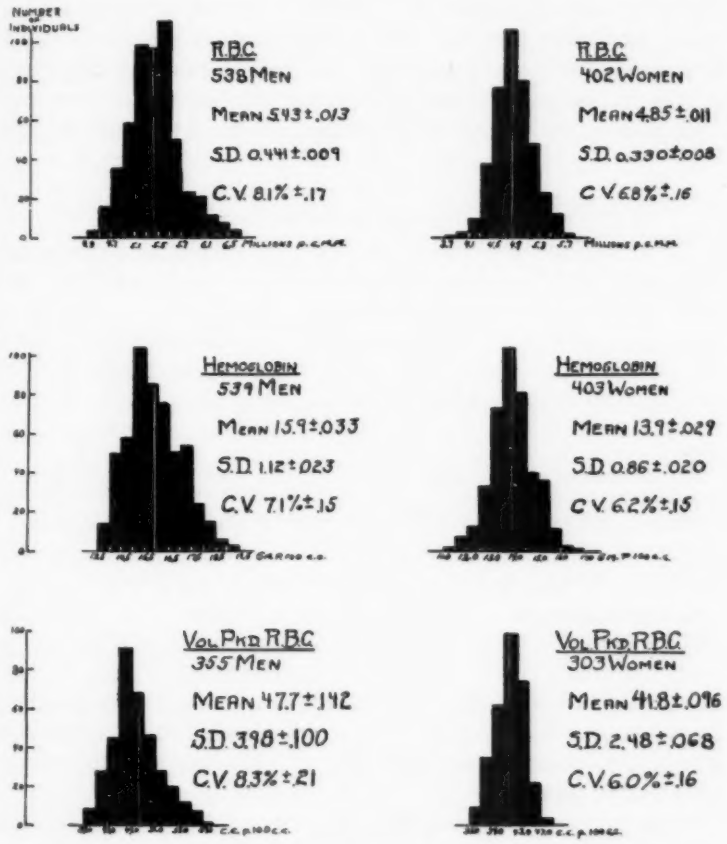

FIG. 2. FREQUENCY DISTRIBUTION OF RED CELL COUNTS, HEMOGLOBIN AND VOLUME OF PACKED RED CELLS AS DETERMINED ON MEN AND WOMEN IN VARIOUS PARTS OF THE UNITED STATES AND EUROPE

S.D. = standard deviation, C.V. = coefficient of variation. The position of the mean is indicated by the white line.

count, hemoglobin and volume of packed red cells, a statistical analysis has been made of these values as reported by a number of observers (1, 5, 6, 9, 11, 12, 14, 15) and to this group the blood examinations recorded in this communication have been added. A few obviously erroneous blood counts have been discarded, but otherwise all reported values have been included. The values for hemoglobin used have been those which correspond to the Van Slyke method of hemoglobinometer calibration. Volume of packed red cells has been calculated to correspond to the volume in heparinized blood. The results of this

TABLE IV

The blood of normal men and women

	NORMAL	RANGE OF NORMAL	PROPORTION OF NORMAL INDIVIDUALS FALLING OUTSIDE THE RANGE GIVEN	
			According to standard deviations for all data (fig. 2)	According to standard deviations for data in figure 1
			per cent	*per cent*
Men:				
Red cell count, millions per c.mm.	5.4	4.6–6.2	6.9	0.004
Hemoglobin, grams per 100 cc.	16	14–18	7.3	2.6
Volume packed red cells, cc. per 100 cc.	47	40–54	7.8	0.05
Women:				
Red cell count, millions per c.mm.	4.8	4.2–5.4	6.8	0.1
Hemoglobin, grams per 100 cc.	14	12–16	2.0	1.2
Volume packed red cells, cc. per 100 cc.	42	37–47	4.4	1.7

analysis are shown in figure 2. It will be seen that the mean values for this large series of determinations correspond closely with those for the smaller series here reported (fig. 1). The variation is, as may be expected, greater.

Using the data given in figures 1 and 2 as a guide, I have selected a series of values which, it seems to me, may safely be employed as the mean and range of normal for red cell count, hemoglobin, and volume of packed red cells in healthy men and women. As nearly as possible, simple numbers have been chosen so that they may easily be remembered. These values are presented in table IV. The proportion of

normal individuals which may be expected to fall outside the limits given, as calculated from the relation of these deviations to the mean (2), is also shown. Judging by the standard deviations of the data recorded in various parts of the world (fig. 2), 2.0 to 7.8 per cent of normal individuals should be found whose blood values would not fall within these limits. According to the standard deviations of the blood examinations reported in this paper (fig. 1) 0.004 to 2.6 per cent of normal individuals would be found to have blood values outside these limits. Considering the nature of the data, I believe the limits of normal presented in table IV are quite adequate.

THE EQUIVALENT OF ONE HUNDRED PER CENT HEMOGLOBIN

The great variation in the values employed as the equivalent of 100 per cent hemoglobin by the different hemoglobinometers reflects the inadequate basis on which these standards have been chosen. The Haldane (8) standard (13.8 grams), formerly much in vogue, was based on the examination of 12 men. More recently the Williamson (13) standard of 16.92 grams has been employed. This is based on a large series of observations but is open to the objection that it represents only the mean value in men and takes no account of the hemoglobin content of the blood of women.

In order that the color index, as calculated from the per cent of hemoglobin, be 1.0 in normal individuals, it is necessary to choose that value of hemoglobin which corresponds, in women as well as in men, to 5.0 million red cells. It is not logical, then, to employ the Williamson standard above mentioned, or the mean values for hemoglobin in men and women which are given in table IV, because the normal mean red cell counts in the two sexes are, respectively, above and below 5.0 million cells.

In an earlier communication (16) it was suggested that 14.5 grams be employed as the equivalent of 100 per cent hemoglobin. This value was derived by calculating the number of grams of hemoglobin equivalent to a count of 5 million red cells as indicated by a number of accurate blood determinations in men and in women published up to that time. When the values published since that time (4, 12), together with the data recorded in this paper, are added to those previously reviewed, the same hemoglobin coefficient as originally proposed is found.

While it is not the purpose of this communication to discuss the advantages of reporting hemoglobin in grams instead of per cent and of calculating the mean hemoglobin content of the red corpuscles in absolute rather than in relative terms (mean corpuscular hemoglobin instead of color index (17)), it may be pointed out that much of the confusion which has arisen concerning the meaning of 100 per cent hemoglobin, and the general lack of understanding of the significance of the color index, may be attributed to the unfortunate attempt to express hemoglobin in per cent. There is more reason to express other chemical constituents of the blood in proportion to an arbitrary normal than there is for expressing hemoglobin in this way, for at least there are slight or no differences between the sexes in these other chemical constituents. Nevertheless, a custom which it is difficult to unroot, has ruled that we remember the normal values for urea nitrogen and creatinine in absolute terms but that it is too difficult to remember the normal values for hemoglobin in grams. As Emerson (3) long ago pointed out, there is no more justification for expressing hemoglobin in proportion to the normal than number of red cells. There is a wide inter-individual and sexual variation in both, and both should be expressed in absolute terms.

SUMMARY

1. Red cell counts, hemoglobin and volume of packed red cells in 229 individuals are reported.

2. These data are analyzed from the standpoint of the places of residence of the subjects, and the question of geographic variation in normal blood values is discussed.

3. Data are collected and analyzed with the view of establishing normal blood values in adults.

4. The advantages of recording hemoglobin in grams instead of per cent are mentioned.

CONCLUSIONS

1. As the result of an analysis of several hundred accurate blood determinations reported from various parts of the United States and Europe, it is concluded that,

a. There appears to be no geographic variation in normal blood

values, and no significant variation with age after adult life is reached, such as would preclude the establishment of normal blood values.

b. The following should be considered the normal values for the blood of adults:

(1) *Red cell count:* men, average 5.4 million with 4.6 to 6.2 million as the limits of normal; women, average 4.8 million, ranging from 4.2 to 5.4 million.

(2) *Hemoglobin:* men, average 16 grams per 100 c.c. of blood, with 14 to 18 grams as the limits of normal; women, average 14 grams, ranging from 12 to 16 grams.

(3) *Volume of packed red cells:* men, average 47 c.c. per 100 c.c. of blood, with 40 to 54 c.c. as the limits of normal; women, average 42 c.c., ranging from 37 to 47 c.c.

c. *If* hemoglobin must be expressed in per cent, 14.5 grams per 100 c.c. of blood should be used as the equivalent of 1.0 per cent.

2. It is preferable to express hemoglobin in grams rather than in per cent.

REFERENCES

(1) Bie, V., and P. Möller: Constitution du sang humain normal. *Arch. d. mal. du coeur*, **15**, 177–205, 1922.

(2) Dunn, H. L.: Application of Statistical Methods in Physiology. *Physiol. Rev.*, **9**, 275–398, 1929.

(3) Emerson, C. P.: The Blood of Normal Young Adults. *Bull. Johns Hopkins Hosp.*, **18**, 29–33, 1907.

(4) Foster, P. C., and J. R. Johnson: Oxygen Capacity and Hemoglobin Content of Normal Blood of Men. *Proc. Soc. Exp. Biol. and Med.*, **28**, 929–932, 1931.

(5) Gram, H. C., and A. Norgäard: Relation between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects. *Arch. Int. Med.*, **31**, 164–170, 1923.

(6) Haden, R. L.: Accurate Criteria for Differentiating Anemias. *Ibid.*, **31**, 766–780, 1923.

(7) Haden, R. L.: Hemoglobin Standards. *Am. J. Clin. Path.*, **3**, 85–95, 1933.

(8) Haldane, J., and J. L., Smith: The Mass and Oxygen Capacity of the Blood in Man. *J. Physiol.*, **25**, 331–343, 1900.

(9) Horneffer, L.: Das Blut des Menschen mit neueren Methoden untersucht. *Arch. f. d. ges. Physiol.*, **220**, 703–737, 1928.

(10) Jenkins, C. E., and C. S. D. Don: The Haemoglobin Concentration of Normal English Males and Females. *J. Hyg.*, **33**, 36–41, 1933.

(11) OSGOOD, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards. *Arch. Int. Med.*, **37**, 685–706, 1926.

OSGOOD, E. E., AND H. D. HASKINS: Relation between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women. *Ibid.*, **39**, 643–655, 1927.

(12) PRICE-JONES, C.: The Concentration of Haemoglobin in Normal Human Blood. *J. Path. and Bacteriol.*, **34**, 779–787, 1931.

(13) WILLIAMSON, C. S.: Influence of Age and Sex on Hemoglobin. *Arch. Int. Med.*, **18**, 505–528, 1916.

(14) WINTROBE, M. M., AND M. W. MILLER: Normal Blood Determinations in the South. *Arch. Int. Med.*, **43**, 96–113, 1929; Hemoglobin Standards in Normal Men. *Proc. Soc. Exper. Biol. and Med.*, **26**, 848–851, 1929.

(15) WINTROBE, M. M.: Blood of Normal Young Women Residing in a Subtropical Climate. *Arch. Int. Med.*, **45**, 287–301, 1930.

(16) *Idem:* The Erythrocyte in Man. *Medicine*, **10**, 195–255, 1930.

(17) *Idem:* The Size and Hemoglobin Content of the Erythrocyte. *J. Lab. and Clin. Med.*, **17**, 899–915, 1932.

(18) *Idem:* Macroscopic Examination of the Blood. *Am. J. Med. Sc.*, **185**, 58–72, 1933.

RECENT KNOWLEDGE REGARDING THE PHYSIOLOGY OF THE GLOSSOPHARYNGEAL NERVE IN MAN WITH AN ANALYSIS OF ITS SENSORY, MOTOR, GUSTATORY AND SECRETORY FUNCTIONS

FREDERICK LEET REICHERT AND EDGAR J. POTH[1]

San Francisco, Cal.

From the Department of Surgery, Stanford University School of Medicine

Submitted for publication May 31, 1933

Since Dandy's publication (1), in 1927, of the sensory and gustatory findings following intracranial section of the glossopharyngeal nerve in patients suffering from tic douloureux of that nerve, identical observations have been recorded by Stookey (2) Reichert (3, 5, 6) and Bailey (4). Fay (7) cut this nerve intracranially for cancer of the tongue and was led to believe from the findings in this case, and in that of another carcinomatous patient in whom he sectioned the vagus nerve, that the sensory changes observed by Dandy were produced by division of the vagus and not by section of the glossopharyngeus. Fay's findings have not been confirmed, but those of Dandy have been amply substantiated.

Dandy's report records a striking physiological experiment in man. Stookey's first case (2) and also that of Reichert (3) were both somewhat complicated by damage to the upper fibers of the vagus nerve. Intracranial section of the ninth nerve in man produces a permanent loss of tactile sensation over the unilateral half of the uvula, soft palate, posterior pharyngeal wall from the eustachian tube to the tip of the epiglottis, over the lateral pharngeal wall and tonsillar region to the anterior pillars and over the unilateral posterior third of the tongue where taste is also lost (fig. 1). Sensory losses over the ear or in the auditory canal could not be demonstrated consistently.

The relatively few fibers of the stylopharyngeus muscle innervated by the ninth nerve are continuous with the fibers of the palatopharyn-

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geus muscle, innervated by the tenth nerve, and for this reason a diagnosis of ninth nerve palsy cannot be made from observation of the movements of the pharynx and soft palate. Electrical stimulation in

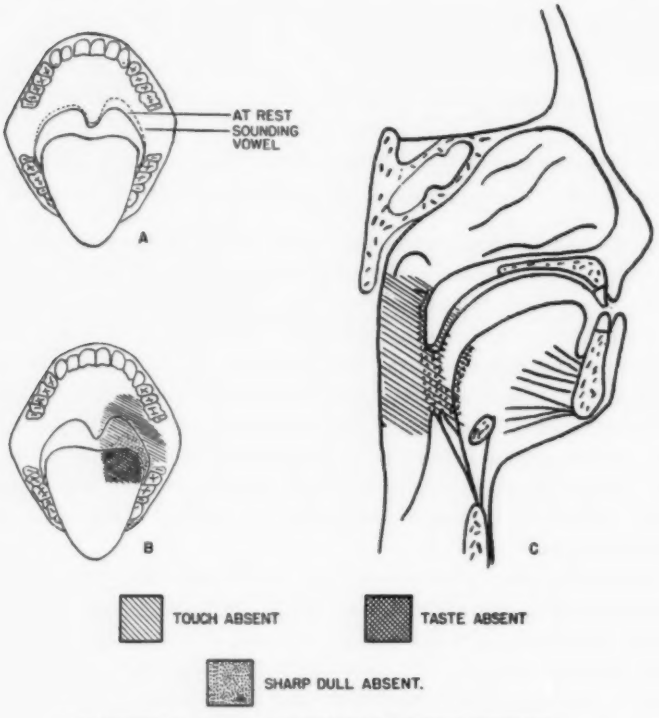


FIG. 1. SENSORY AND GUSTATORY CHANGES AFTER INTRACRANIAL DIVISION OF THE GLOSSOPHARYNGEAL NERVE

No motor disturbance of the soft palate was observed

one of Reichert's cases (Case II (5)) suggested a slightly weakened response attributable to this muscle. When the upper fibers of the vagus are traumatized, as occurred in Stookey's and in Reichert's

patient, a definite lowering of the soft palate and difficulty in swallowing very large boluses of food were observed. These abnormalities have disappeared within a year in Reichert's patient, while the loss of taste has been permanent over the unilateral pharynx and posterior third of the tongue as far as the circumvallate papillae.

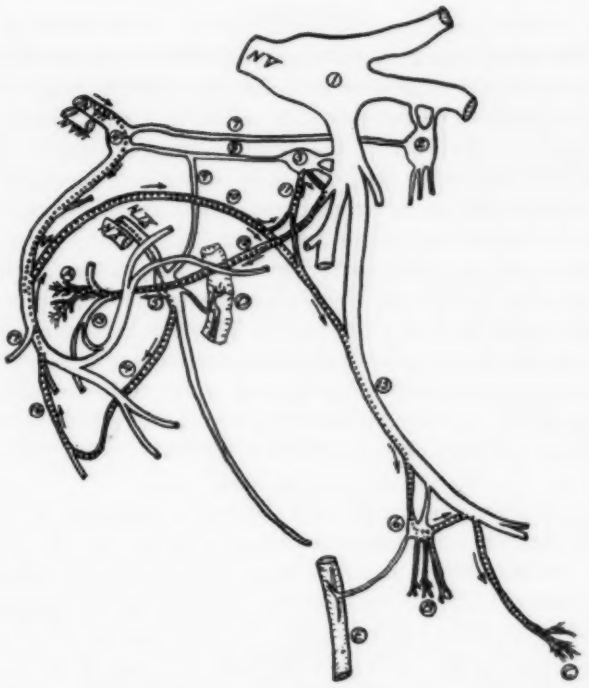
The activity of the salivary glands has been studied in three of our patients (8) over periods varying from ten days to two and a half years after division of the ninth nerve. Accurate and simultaneous measurements of the rate of secretion of the parotid and of the submaxillary glands were obtained by the method of Poth (9) and showed a marked, immediate diminution of salivation on the side on which the nerve had been cut. Within three months after operation the secretion from these glands had increased in amount but continued to be definitely less than that of the normal side. These results indicate that at least part of the secretory fibers to the salivary glands come from the brain along the ninth nerve.

Through the courtesy of Drs. Sewall, Bacher, Cowan and Borden of the Otolaryngological Department collections were made of the salivary secretions of four patients in whom the chorda tympani had been divided just distal to the facial canal in the course of performing radical mastoidectomies. Careful observations during operation made it certain that the tympanic nerve, a branch of the glossopharyngeus, was not injured, except possibly its terminal filaments in the eustachian tube. All of these patients showed a loss of taste on the corresponding unilateral anterior half to two-thirds of the tongue. It has been definitely established by Lewis and Dandy (10) that taste fibers from the anterior two-thirds of the tongue run in the chorda tympani and facial nerve to the brain. These patients (8) were studied during periods of three days to four months after radical mastoidectomy and showed a marked and permanent diminution of salivation on the involved sides. Partial recovery of secretory activity after section of the ninth nerve intracranially indicates that all of the secretory fibers do not arise from this source. And since section of the chorda tympani results in a permanent marked diminution in secretory rate, the secretory fibers from both the seventh and ninth nerves must be collected together in this branch of the facial nerve. The secretory fibers from the ninth nerve might join the seventh nerve by two differ-

ent peripheral pathways. They might leave the petrous ganglion and reach the facial nerve by way of the tympanic and small superficial petrosal nerves and join the facial nerve in the region of the geniculate ganglion to run through the facial canal, and so enter the chorda tympani. Or they might leave the petrous ganglion by way of the anastomosing branch of the glossopharyngeal nerve to join the auricular branch of the seventh nerve, then running cephalad to enter the chorda tympani.

That the first of these pathways is unlikely is evident from the following observations. Hesse (11) sectioned the ninth nerve in the neck, without doubt distal to the petrous ganglion, and showed that secretory activity of the parotid gland on the corresponding side was diminished. A case of Bell's palsy with taste intact (the lesion was probably at the stylomastoid foramen distal to the junction of the facial nerve and chorda tympani), of five weeks' duration, showed a decreased secretory rate of all the salivary glands on the corresponding side. Also, in one case of neuralgia of Jacobson's plexus so far reported (6) salivation was not a part of the clinical picture, as would have been the case if the secretory fibers had run through the tympanic plexus. Not only are Hesse's observations, and the experimental evidence gained from the study of the case of Bell's palsy, against a pathway through the tympanic plexus, but they offer support for a course through the anastomosing branch of the glossopharyngeal to the facial nerve.

Therefore, the most probable pathway for the secretory fibers from the glossopharyngeal nerve is that they leave by way of the anastomosing branch to the auricular branch of the seventh nerve, then continue cephalad in the facial nerve, and enter the chorda tympani nerve together with the secretory fibers from the seventh nerve. Fibers from both the seventh and ninth nerves run peripherally to supply the three sets of salivary glands. Those to the parotid gland go by way of the otic ganglion to the auriculo-temporal branch of the fifth nerve. Those to the sublingual and submaxillary glands continue with the chorda tympani to join the lingual branch of the fifth nerve, and thence by way of the submaxillary ganglion to the respective glands (fig. 2).



MODIFIED FROM LEWIS AND DANDY LOC. CIT. 1. GASSERIAN GANGLION. 2. MECKEL'S GANGLION. 3. OTIC GANGLION. 4. GENICULATE GANGLION. 5. PETROUS GANGLION. 6. SUBMAXILLARY GANGLION. 7. GREAT SUPERFICIAL PETROSAL NERVE. 8. LESSER SUPERFICIAL PETROSAL NERVE. 9. TYMPANIC NERVE. 10. CHORDA TYMPANI. 11. ANASTOMOSIS BETWEEN OTIC GANGLION AND CHORDA TYMPANI. 12. AURICULOTEMPORAL NERVE. 13. COMMUNICATING BRANCH OF AURICULOTEMPORAL AND FACIAL NERVES. 14. ANASTOMOSING BRANCH OF GLOSSOPHARYNGEAL NERVE WITH DIGASTRIC BRANCH OF FACIAL NERVES. 15. LINGUAL NERVE. 16. DIGASTRIC BRANCH OF FACIAL NERVE. 17. POSTERIOR AURICULAR NERVE. A. PAROTID GLAND. B. SUBMAXILLARY GLAND. C. SUBLINGUAL GLAND. D. INTERNAL CAROTID ARTERY WITH SYMPATHETIC FIBERS TO PETROUS GANGLION. E. FACIAL ARTERY WITH SYMPATHETIC FIBERS TO SUBMAXILLARY GANGLION.

FIG. 2. NEW PATHWAYS FOR THE SECRETORY FIBERS TO THE SALIVARY GLANDS

Secretory fibers from the ninth nerve pass by an anastomosing branch to the auricular branch of the seventh nerve, then cephalad in the facial nerve to enter the chorda tympani together with the secretory fibers from the seventh nerve.

DISCUSSION

In the anatomical and neurological textbooks there is a general agreement that the ninth nerve innervates the stylopharyngeus muscle. From observations on patients with cerebellar tumors, some authors have described deviation of the pharynx, lowered palatal arch and difficulty in swallowing attributable to paralysis of the ninth nerve. They assume that the nerve also innervates the superior constrictor, palato-pharyngeus and palato-glossus muscles. Partial vagal paralysis undoubtedly occurred along with the glossopharyngeal weakness in the patients with tumors, which led to the erroneous conclusions as to the motor function of the ninth nerve. They obtained anatomical substantiation for this extensive motor function from the fact that pharyngeal branches of the glossopharyngeal unite with the pharyngeal branches of the vagus and sympathetic to form the pharyngeal plexus. Branches from the plexus perforate the muscular coat of the pharynx and supply its muscles and mucous membrane.

There is general agreement that the glossopharyngeus nerve is the nerve of ordinary sensation to the mucous membrane of the pharynx, fauces, palatine tonsil, posterior third of the tongue and tympanic cavity, mastoid cells and auditory tube. Hunt (12) felt from his studies of patients with aural herpes that this nerve had an irregular area of innervation in the external auditory canal and on the auricle itself. Fay (13), by stimulation of the vagus and hypoglossal nerves, found his patients complained of pain in the pharynx, tonsillar fossa and base of the tongue, and was led to believe that the sensory fibers of the vagus innervated the mucous membrane of this region, particularly in regard to deep sensation. Loss of tactile sensation after intracranial section of the ninth nerve showed, in the areas available for testing, a sensory disturbance that was more accurately delineated but in general agreement with those described in anatomical works (fig. 1).

Gustatory sense over the posterior third of the tongue has always been attributed to the glossopharyngeus and, on section of the nerve, taste is lost over half of the posterior portion of the tongue.

That the glossopharyngeus nerve carries secretory fibers to the parotid gland through a devious pathway is described in all texts which also state that the fibers to the sublingual and submaxillary salivary

glands come from the facial nerve through the chorda tympani. From observations made on the salivary secretion in the dog the following statement from Howell's textbook (14) presents the current knowledge.

> These glands receive their nerve supply from two general sources,—namely, the bulbar autonomics (or cerebral fibers) and the sympathetic autonomics. The parotid gland receives its bulbar autonomics from the glossopharyngeal or ninth cranial nerve; they pass into a branch of this nerve, known as the tympanic branch or nerve of Jacobson, thence to the small superficial petrosal nerve, through which they reach the otic ganglion. From this ganglion they pass (postganglionic fibers) by way of the auriculotemporal branch of the inferior maxillary division of the fifth cranial nerve to the parotid gland. The sympathetic autonomics pass to the superior cervical ganglion by way of the cervical sympathetic, and thence as postganglionic fibers in branches which accompany the arteries distributed to the gland. The bulbar autonomic supply for the submaxillary and sublingual glands arises from the brain in the facial nerve and passes out in the chorda tympani branch. This latter nerve after emerging from the tympanic cavity through the Glaserian fissure, joins the lingual nerve. After running with this nerve for a short distance, the secretory (and vasodilator) nerve fibers destined for the submaxillary and sublingual glands branch off and pass to the glands, following the course of the ducts. . . . The supply of sympathetic autonomics has the same general course as those to the parotid.

Our observations from accurate simultaneous collections of parotid and submaxillary salivary secretions in three patients, after intracranial division of the ninth nerve, revealed an immediate and marked diminution in secretion of these glands which again approached that of the normal side by the third postoperative month. When the chorda tympani has been sectioned just distal to its exit from the facial canal the secretions from the salivary glands were markedly and permanently diminished. This evidence indicates that the three salivary glands in man, parotid, submaxillary and sublingual, receive their secretory fibers from both the seventh and ninth nerves.

Furthermore, the observations of Hesse that parotid secretion is diminished after section of the ninth nerve high in the neck and extracranially, and our examination of a case of peripheral facial palsy with normal taste over the anterior portion of the tongue but with marked diminution of the secretions from the salivary glands permits only one pathway for the secretory fibers from the ninth nerve to run and unite with those of the seventh nerve in the chorda tympani. This pathway

is through an anastomosing branch arising from the trunk of the glossopharyngeus below the petrous ganglion which joins the facial just after the exit of the nerve from the stylomastoid foramen (fig. 2).

CONCLUSIONS

Intracranial division of the glossopharyngeal nerve in man for tic douloureux has afforded more accurate knowledge of the sensory, motor, gustatory and secretory functions of this nerve.

In the areas available for examination the sensory distribution of the ninth nerve was accurately delineated, and indicated a unilateral loss of tactile sensation of the nasopharynx, soft palate, tonsillar region and posterior pharyngeal wall from the eustachian tube to the tip of the epiglottis. Sensory losses over the ear or in the external auditory canal could not be demonstrated consistently.

Because of the relatively few fibers of the stylopharyngeus muscle, innervated by the ninth nerve, as compared with the number of fibers contributed by the palatopharyngeus muscle, innervated by the tenth nerve, no motor disturbances can be shown after section of the ninth nerve intracranially.

Taste is permanently lost over the unilateral posterior third of the tongue after interruption of the glossopharyngeal nerve.

Contrary to accepted teaching, section of the ninth nerve intracranially causes marked temporary diminution of salivation with partial recovery involving parotid, sublingual and submaxillary glands.

Other evidence is submitted which reveals that in man the salivary glands receive their secretory fibers from both the seventh and ninth nerves.

The most probable course of the salivary secretory fibers from the ninth nerve is by way of the anastomosing branch to the auricular branch of the seventh nerve, then cephalad in the facial nerve to enter the chorda tympani nerve together with the secretory fibers from the seventh nerve.

REFERENCES

(1) Dandy, W. E.: Glossopharyngeal Neuralgia (Tic Douloureux). Its Diagnosis and Treatment. *Arch. Surg.*, vol. 15, p. 198, Aug. 1927.

(2) Stookey, B.: Glossopharyngeal Neuralgia. Surgical Treatment, with Remarks on the Distribution of the Glossopharyngeal Nerve. *Arch. Neurol. and Psychiat.*, vol. 20, p. 702, Oct. 1928.

(3) REICHERT, F. L.: Glossopharyngeal Neuralgia. *West. Jour. Surg.*, vol. 39, p. 347, May, 1931.

(4) BAILEY, P.: Neuralgias of the Cranial Nerves. *Surg. Clin. N. Amer.*, vol. 11, p. 61, Feb. 1931.

(5) REICHERT, F. L.: Three Cases of Glossopharyngeal Neuralgia Cured by Intracranial Section of the Nerve. *Ibid.*, vol. 13, p. 193, Feb. 1933.

(6) *Idem:* Tympanic Plexus Neuralgia (True Tic Douloureux of the Ear or so-called Geniculate Ganglion Neuralgia). Cure Effected by Intracranial Section of the Glossopharyngeal Nerve. *J. A. M. A.*, vol. 100, p. 1744, June 3, 1933.

(7) FAY, T.: Observations and Results from Intracranial Section of the Glossopharyngeus and Vagus Nerves in Man. *Jour. Neurol. and Psychopath.*, vol. 8, p. 110, Oct. 1927.

(8) REICHERT, F. L. AND E. J. POTH: Pathways for the Secretory Fibers of the Salivary Glands in Man. *Proc. Exper. Biol. and Med.*, vol. 30, p. 973, April, 1933.

(9) POTH, E. J.: A Simplified Technique for the Quantitative Collection of the Salivary Secretions of Man. *Ibid.*, vol. 30, p. 977, April, 1933.

(10) LEWIS, D. AND W. E. DANDY. The Course of the Nerve Fibers Transmitting Sensations of Taste. *Arch. Surg.*, vol. 21, p 249, Aug. 1930.

(11) HESSE, E.: Ueber die Chirurgische Behandlung der genuinen Glossopharyngeus Neuralgie. *Verhandl. d. Russ. Chir. Trilogov. Gesellsch.*, 1930. (*Internat. Abst. Surg., Surg. Gyn. and Obst.*, vol. 52, p. 114., Feb. 1931.)

(12) HUNT, J. RAMSAY: The Symptom-Complex of the Acute Posterior Poliomyelitis of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia. *Arch. Int. Med.*, vol. 5, p. 631, 1910.

(13) FAY, T.: Atypical Facial Neuralgia, a Syndrome of Vascular Pain. *Ann. Otol. Rhinol. and Laryngol.*, vol. 41, p. 1030, Dec. 1932.

(14) HOWELL, W. H.: A Text-book of Physiology. W. B. Saunders Co., Phila. 9th Ed. p. 755, 1926.

THE RÔLE OF VENTRICULAR DILATATION IN THE SPREAD OF INFECTIONS FROM THE SUBARACHNOID SPACE INTO THE VENTRICLES

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Infections of the ventricles have been observed to follow primary infections of the meninges. In their discussion of the pathogenesis of tuberculous meningitis, Rich and McCordock (3) have pointed out that primary tuberculosis of the cranial meninges often leads to tuberculous infection of the ependyma lining the cerebral ventricles. These findings are difficult to reconcile with the generally accepted view that there is a steady flow of cerebrospinal fluid from the ventricles into the subarachnoid space; and tubercles of the ventricular ependyma, probably in part because of this, have been thought to occur only when bacilli pass from the blood through the chorioid plexus into the ventricles. Abundant evidence from the studies of Rich and McCordock, however, demonstrate that tuberculosis of the ventricles occurs in the absence of blood-stream infection and must be accounted for by a retrograde passage of bacilli from the subarachnoid space.

The problem arising from these observations is to define the forces responsible for movement of bacteria or other foreign matter from the subarachnoid space into the ventricles. In experiments having to do with measurement of the rate of formation of cerebrospinal fluid (2), it was noted that the steady flow of fluid from the ventricles was at times interrupted by rapid suction of fluid into the ventricles or rapid expulsion of fluid from them. These sudden changes in rate and direction of fluid-flow are thought to be the result of changes in the volume of the ventricles. We are particularly interested here in increase of ventricular volume, in the change in direction of cerebrospinal fluid-flow which occurs when the ventricles dilate and fluid is sucked from the subarachnoid space into them. A quantitative understanding of this point requires knowledge of the volumes of the ventricles and the

subarachnoid space, as well as of the magnitude of ventricular dilatation.

THE VOLUMES OF THE VENTRICLES AND OF THE SUBARACHNOID SPACE

All the observations to be given here have come from experiments on adult cats of quite uniform size. Their weights varied between 2500 and 3500 gm. and their lengths, from the vertex of the skull to the last lumbar spine, from 36 to 41 cm.

The volume of the third and lateral ventricles in these cats has been measured by a modification of the procedure already reported in detail (2): After exposure of the cerebellum and cisterna magna, a small catheter, surrounded by a rubber balloon, was inserted into the fourth ventricle and against the aqueduct of Sylvius. To secure blockage of the ventricle, the balloon was then dilated and the catheter was connected by way of a bubble-manometer to a fluid reservoir kept at a pressure of approximately 110 mm. water, the average normal intraventricular pressure for adult cats (5).

After killing the animal with ether or by puncturing its medulla, the calvarium was quickly removed. The fluid reservoir was then shut off, with the catheter and its balloon still in place. By this procedure the ventricles had been filled with fluid at normal pressure and the fluid retained therein. One lateral ventricle was carefully entered by cutting through one of the cerebral hemispheres near the mid-line, and the fluid within it was absorbed on a previously weighed cotton pledget. In the same way the fluid in the third ventricle and in the other lateral ventricle was absorbed on cotton. The difference in weight of the dry cotton and the wet cotton gave a fair estimate of the volume of the lateral and third ventricles. In six cats, these measurements gave an average ventricular volume of 0.7 cc. with extremes of 0.6 cc. and 0.9 cc.

The volume of the fourth ventricle has been measured in a different way. In three cats, immediately after death, the cisterna magna and the caudal portion of the cerebellum were exposed. The fourth ventricle was then filled with paraffin of low melting point from a needle placed from the cisterna magna into the fourth ventricle and against the aqueduct. Two errors entered into this method. First, the cerebellum had to be slightly elevated in order to bring the opening

of the aqueduct into view and to place the needle suitably for the injection of paraffin. This error has been minimized by permitting the cerebellum to drop back into a position approaching normal after the injection and while the paraffin was still liquid. Second, a perfect cast of the ventricle was not given by paraffin because it contracts on cooling. Neither of these errors appeared to be substantial, however, and the magnitude of either was diminished by the compensation of the other. It was consequently possible to gain a rather exact estimate of the volume of this ventricle by measuring the volume of alcohol displaced by the paraffin cast. These determinations, made in duplicate on each animal, gave an average value of 0.2 cc. for the volume of the fourth ventricle with extremes of 0.2 and 0.3 cc.

There has been great difficulty in measuring the volume of the subarachnoid space. Several methods have been used; all contain errors so apparent that they need no detailed discussion. The simplest and most direct method is to do combined lumbar and cisternal punctures and to collect and measure the cerebrospinal fluid which flows from the cisternal needle when air is introduced into the lumbar needle. To change the animal's position from the horizontal to the two vertical positions is also of advantage in this procedure. There is in this method, however, no way of knowing that the air has completely displaced the fluid nor that a considerable portion of ventricular fluid has not been added to that from the subarachnoid space. A second method, even less reliable than that just described, consists of a determination of the difference between total intradural volume (1) and the volume of the brain and spinal cord. And finally, an effort has been made to measure the volume of the subarachnoid space by killing an animal with ether, placing its body in a freezing chamber and, 24 hours later, removing the ice from the subarachnoid space. Not only is it unlikely that all the ice will be recovered from the subarachnoid space but it is almost certain that such a large change in the distribution of fluids occurs with death and after death as to make the method practically without value.

These three methods have yielded values for the volume of the subarachnoid space in cats of the rather uniform size mentioned which vary between 1.5 cc. and 4.0 cc. The lower values came from the freezing method and the method involving the difference between

intradural and central nervous system volumes and, as has been stated, are of very questionable meaning. The higher values from the air-displacement method have, in six animals, varied between 2.4 cc. and 4.0 cc. with an average value of 3.5 cc. The average intradural volume in a series of cats of much the same size and age has been found to be 34 cc. (4), and it is interesting to note that in cat as in man the air-displacement method gives a value for the volume of the subarachnoid space about 10 per cent that of the total intradural contents.

With this datum it is possible now to calculate approximately the average volume of a unit length of subarachnoid space. The cats used here had an average length, from vertex to last lumbar spine, of 39 cms.; the total volume of the subarachnoid space was found to be 3.5 cc. An average segment of subarachnoid space, therefore, has a volume of 0.09 cc. per cm. length. There are, in the subarachnoid space, quite obviously, wide variations from this average due to the cisternae about the brain and the variations in volume of different segments of the spinal cord, but no measurements are available which permit their evaluation.

CHANGES OF VENTRICULAR VOLUME

In a study of the rate of formation of cerebrospinal fluid, it was noted (2) that beyond the small and regular changes in volume of the third and lateral ventricles which occurred with the heart beat and respiration, relatively large amounts of fluid were at intervals suddenly sucked into or expelled from the ventricles. In some experiments as much as 0.1 cc. of fluid was aspirated into the ventricles in the course of one minute; and in other animals it was noted that as much as 0.3 cc. of fluid, within half a minute, was suddenly expelled from the ventricles. At times the original ventricular volume was quickly reëstablished but often the changes were maintained for some time.

Simultaneous measurement of intracranial arterial and venous pressures and of cerebrospinal fluid-flow furnished data which appeared to offer an explanation of these observations. The changes in arterial pressure likely to occur in the course of a well conducted ex-

periment, with the animal in good condition, did not alter in an appreciable way the rate of flow. Rather marked changes in venous pressure occurring without apparent cause or, on occasion, as a result of movement of the animal were, however, usually associated with changes in the rate of flow. Sharp increases in venous pressure were accompanied by expulsion of fluid from the ventricles due, in part it appeared, to an increase in the blood volume of their walls and hence to a decrease in ventricular volume. Decrease in venous pressure, on the other hand, was accompanied by aspiration of fluid into the ventricles due, apparently, to a decrease in the blood volume of their walls and hence an increase in ventricular volume. These observations have been discussed in more detail elsewhere (2).

DISCUSSION

The findings given above have been presented in an effort to understand the retrograde passage of foreign matter, bacteria, etc., from the subarachnoid space into the ventricles. It has been pointed out that, in etherized cats, as much as 0.1 cc. of fluid may be aspirated into the ventricles. Small though this quantity of fluid may at first appear to be, its significance is appreciated when it is compared with the volume of the ventricles and with the volume of the subarachnoid space.

The average volume of the fourth ventricle has been found to be 0.2 cc. An increase in volume of all the ventricles amounting to 0.1 cc. consequently aspirates into the fourth ventricle from the subarachnoid space a quantity of fluid equal to one-half of the original volume of the ventricle. If tubercle bacilli, for example, be present in the fluid from the subarachnoid space, they may thus come in contact with the walls of the ventricles, become implanted and grow there. In subsequent fluctuations of ventricular volume, fluid will be aspirated from the fourth ventricle into the third and lateral ventricles, and at autopsy, as found by Rich and McCordock, all the ventricles will be found to be studded with tubercles. That the small increases in ventricular volume noted here cause a significant flow of fluid into the third and lateral ventricles is clear, in view of the small volume of these ventricles which averages only 0.7 cc.

Ventricular volume changes probably also cause a considerable movement of fluid in the subarachnoid space and so are of some importance in the spread of lesions there. It has been found that a segment of subarachnoid space 1 cm. long and with a circumference equal to the average circumference of the space has a volume of 0.09 cc. If the subarachnoid space were to be regarded as a tube of fixed dimensions open at one end, a ventricular dilatation of 0.1cc. would cause an average movement of fluid of 1 cm. in length and the maximal expulsion of fluid noted here, 0.3 cc., would cause an average displacement of fluid of over 3 cm. The subarachnoid space is, however, more complex than this. Its volume varies with intradural blood volume changes in much the same way as does that of the ventricles; but any statement beyond this must be purely speculative. Suffice it for the moment to reiterate in a qualitative way that ventricular volume changes probably cause a significant movement of fluid in the subarachnoid space.

It should be emphasized that these observations have been made on anesthetized animals. In conscious animals, moving about, intracranial venous pressure changes and hence ventricular volume changes probably occur more frequently and are of greater magnitude than in the etherized laboratory mammals. It is to be supposed, consequently, that in active animals and in man quantities of cerebrospinal fluid relatively even larger than those noted here may be aspirated into the ventricles. If the fluid carry with it disease-producing cells, lesions first present in the subarachnoid space may, in this way, be spread into the ventricles.

SUMMARY

Measurements have been made of the volumes of the ventricles and subarachnoid space of the cat and of the quantity of cerebrospinal fluid which may be aspirated from the subarachnoid space into the ventricles by ventricular dilatation. A comparison of these quantities indicates that a significant volume of fluid may be sucked into the ventricles and offers an explanation for the retrograde passage of bacteria and other foreign matter from the subarachnoid space into the ventricles.

BIBLIOGRAPHY

(1) FLEXNER, L. B., J. H. CLARK AND L. H. WEED. 1932. *Am. Jour. Physiol.*, **101**, 292.
(2) FLEXNER, L. B., AND H. WINTERS. 1932. *ibid.*, **101**, 697.
(3) RICH, A. R., AND H. A. MCCORDOCK. 1933. *Bull. Johns Hopkins Hosp.*, **52**, 5.
(4) WEED, L. H., AND L. B. FLEXNER. 1932. *Am. Jour. Physiol.*, **101**, 668.
(5) WEED, L. H., AND W. HUGHSON. 1921. *ibid.*, **58**, 53.

LOCOMOTION OF RAT LYMPHOCYTES IN TISSUE CULTURES

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The lymphocyte is a cell of mystery. Its functions are unknown, its life history is the subject of controversy, its constancy in the normal blood stream is unexplained, its increase in certain diseases and its decrease in others still await solution. There seems to be a general agreement that it is not phagocytic. Murphy and Taylor and Ellis attribute to lymphocytes the resistance of the body to tuberculosis and to transplanted cancer, ignoring the fact that lymph nodes are the favorite sites for tubercles and cancer metastases. Since lymphocytes find their way onto the mucous membranes, especially the intestine (Bunting and Huston), where bacteria are numerous, it has been suggested that they may have an antitoxic action, but this is mere speculation. Since the repeated parenteral injections of various proteins produce, according to Wiseman, a general lymphatic hyperplasia and a lymphocytosis, he suggests that the lymphocytes reduce or neutralize foreign proteins which get into the tissues. They possess no oxidative ferments but are said to contain protein and fat-splitting enzymes.

There are several theories regarding the origin and fate of the lymphocyte with such persistent advocates for each one that they tend to assume a religious significance. The monophylitic cults derive it in common with other white blood cells from a primitive reticular cell. It is impossible, however, to get from the literature a clear idea of this nebulous ancestor. The polyphylitic cults also have imaginative ancestors for it and for the other leucocytes.

Not only is its origin bathed in mystery but its fate also is the subject of religious beliefs that guide it into becoming a red blood cell or a granular blood cell, or a non-granular blood cell or a macrophage and

so on, even to a fibroblast. It is possible, however, that the lymphocyte may represent an independent self-perpetuating strain of cells. It seems evident, especially since the recent work of Wiseman, that the lymphocyte has young and old stages and that the young stages readily undergo division.

For years the lymphocyte was regarded by many as a small round non-motile cell but its appearance in the tissues, even though as a small round cell, led to the assumption of its motility by others. The first demonstration of its rate of locomotion was by Lewis and Webster in 1921. They found that the locomotion of human lymphocytes is characterized (1) by alternating periods of rest and locomotion with change from spherical to elongated forms, (2) by peculiar wavy migratory paths, (3) by changes in speed from moment to moment, and (4) by variations in the average rates of different lymphocytes. During the rest periods the lymphocytes frequently thrust out small pseudopodia and wriggle about a little without any forward progression. They found the average rates for 35 lymphocytes from normal and abnormal human lymph nodes in homo- and autoplasma cultures of various ages varied from 6 to 20 microns per minute. The general average was about 12 microns per minute. McCutcheon, in 1924, found that the rate of locomotion of human lymphocytes in thin spreads of whole blood varied from 4 microns per minute at one hour *in vitro* to 15 microns per minute at 9 hours *in vitro*. Lewis and Webster did not find any significant differences in the rate of migration in the $1\frac{1}{2}$-, 4-, 24-, 48- and 168-hour cultures, but the cells in their cultures were under quite different environmental conditions from those of McCutcheon's spreads.

There is still, however, a general impression that the lymphocytes are only slightly amoeboid and that their locomotion is extremely slow, much slower than the locomotion of the neutrophiles. One glance at the motion pictures of the two types of cells will rapidly dispel any such notion. The rate of locomotion of any particular lymphocyte or neutrophile will depend upon a number of factors such as the temperature, the medium, the *in vitro* conditions, the age of the cell, the metabolic condition of the cell and the age of the preparation. McCutcheon found, as already noted, that the average rate of human lymphocytes in spreads of whole blood increased from 4 microns per minute

in his one-hour preparations to 15 microns per minute in the 9-hour preparations. He also found that the average rate of the neutrophiles in similar preparations varied from 36 to 21 microns per minute and that they tended to decrease rather than increase in speed during the first nine hours. According to his measurements, then, the neutrophiles move from one and a half to several times as fast as the lymphocytes.

Quite different figures are obtained if the rates of locomotion in other types of preparations are compared. For example, in a 5½-hour hanging-drop culture of a rat lymph node in autoplasma the average rate of 48 lymphocytes having 68 periods of locomotion, varying from 30 to 480 seconds in length, was 19.6 microns per minute. The average rate, in a 9½-hour culture from the buffy coat of a rat in autoplasma, of 20 neutrophiles under observation for 3⅓ to 19 minutes each was 19.4 microns per minute. Thus compared, the lymphocytes moved more rapidly than the neutrophiles. In the above cultures the average rate of the different lymphocytes varied greatly; the slowest one migrated at the rate of 9.6 microns per minute and the fastest one at the rate of 35.1 microns. The neutrophiles were more uniform; the minimum rate was 13.6 and the maximum 26.7 microns per minute. Some of the lymphocytes moved more rapidly than any of the neutrophiles.

Locomotion is obviously a complicated affair and all the factors above noted, and probably many others, will have to come into the picture before a clear understanding is obtained. Although the rate of locomotion is variable, the type of locomotion is the same for all the lymphocytes so far investigated. This type of locomotion (Lewis, 1931a), as revealed by motion pictures, is similar to that of the amoeba as described by Mast (1926). The essential features of this are local softening or solation with the formation of a pseudopod at the anterior end due to the contraction of an outer plasmagel layer which forces the inner plasmasol and nucleus forward, while the plasmagel, or that portion of it which on the lymphocyte forms a constriction ring at the base of the pseudopod, remains fixed as regards objects in space. At the posterior end, the inner surface of the outer plasmagel layer is continuously being transformed into the plasmasol which, after being forced forward, is continuously changed again into the plasmagel state

at the continuously advancing anterior rim of the plasmagel tube in front of the constriction ring. After most of the lymphocyte has passed forward through the constriction ring the latter contracts to form a tail-like knob which persists throughout a migratory period. As the lymphocyte moves forward, with persistent anterior and posterior ends, new constriction rings form one after another and accompanying these there are alternations in length and form of the lymphocyte and in the rate of migration.

This study is based on eleven motion pictures (table 1), of rat lymphocytes in ten cultures, three of lymph nodes in autoplasma (films no. 96 and 97 are from the same culture), two of omentum (one in homo- and one in autoplasma), and five of Walker rat sarcoma 338 (three in chicken plasma and two in Gey's medium 3737). The films give permanent and accurate records of various features of migrating cells that cannot otherwise be obtained. The variations in temperature were slight and probably did not appreciably affect the rate of locomotion.

The average rate of locomotion (table 1) for all the lymphocytes charted in each culture varied from 10 microns to 22.6 microns per minute. Neither the age of the culture, within the limits used, nor the culture media utilized had any influence on the rate.

TECHNIC

Ordinary small hanging-drop cultures were used for all the films except 158 and 159. The latter were large drops on large coverglasses. Data regarding the sources of the explants, culture media and age of cultures are given in table 1. At the time the films were made, lymphocytes were migrating about in various directions, some on the coverglass, others deeper down in the plasma clot. Those on the coverglass remained longer in focus than those in the depth of the clot. Some entered the field, others left; some came up to the coverglass and into the focal field, others left the coverglass to go down into the clot out of focus. The microscope was focussed on the cells migrating on the under surface of the coverglass. The "focal field" refers to this focal plane limited by the size of the field on the film, 148 × 109 microns. The initial magnification on the films is 165 diameters. As shown in table 1, the number of frames taken per minute varied

from 3.1 to 24. When such films are projected at the normal speed, 960 frames per minute (F.P.M.), those cells taken at 3.1 F.P.M. will be speeded up 310 times and those at 24 F.P.M. 40 times. As lymphocytes move rapidly the ones taken at 24 F.P.M. are better for observation when the film is projected on the screen at the usual rate than those taken at 3.1 F.P.M. They give, however, only a general idea of the locomotion.

TABLE 1

The number of each film (No.), the number of frames taken per minute (F. P. M.), the length of the film in feet (Ft.), the intervals used for plotting (Int.), the number of lymphocytes measured (Lym.), the number of migratory periods (Per.), the tissue used (Tissue), the age of each culture in hours (Age), the culture media (Medium), and the average rate of locomotion per minute in microns for all the lymphocytes measured in each culture (Rate). The temperature of the warm box containing the culture at the time the film was made was 38.2°C ± 1°.

NUMBER	F. P. M.	FT.	INT.	LYM.	PER.	TISSUE	AGE	MEDIUM	RATE
43	24.0	90	20.0	48	68	Lymph node	5.5	Autoplasma	19.6
96	23.1	63	20.8	10	17	Lymph node	24.0	Autoplasma	16.6
97	23.1	63	20.8	9	19	Lymph node	29.0	Autoplasma	13.1
29	5.3	55	11.32	1	17	Lymph node	30.0	Autoplasma	22.4
37	5.3	93	22.6	2	6	Omentum	24.0	Homoplasma	13.9
38	5.3	78	22.6	1	3	Omentum	48.0	Autoplasma	10.0
156	11.6	117	20.7	1	3	Sarc. 338	24.0	Chicken plasma	12.6
141	3.1	58	19.7	3	4	Sarc. 338	48.0	Chicken plasma	22.6
147	11.6	26	20.7	6	8	Sarc. 338	48.0	Chicken plasma	16.4
158	11.6	19	20.7	1	1	Sarc. 338	96.0	3737-Gey	22.4
159	11.6	19	20.7	1	2	Sarc. 338	120.0	3737-Gey	16.2
General average rate of migration.....									16.5

For detailed study the frames were projected onto paper, and outlines of the lymphocytes drawn. Some of the first tracings were made at 1485 diameters (9 × 165 the magnification of the film); later a magnification of 2000 diameters was adopted. Since the projected image from each frame comes exactly into position as regards the preceding and succeeding ones, a series of outlines of a lymphocyte gives an exact picture of its migratory path and of the distance traversed during intervals between frames. The method is so mechanically exact that the drawings and the film can at any subsequent date be replaced in position and the correctness of the tracings verified. The

method is more accurate than camera lucida outlines or measurements with the eyepiece micrometer. The greatest source of error arises from the difficulty in getting sharp images on the film of the thin advancing pseudopod at the anterior end of the lymphocyte, but this source of error is small and is not accumulative. The number of frames per minute is constant for each film. In plotting the migration paths it was not necessary to use all the frames. Every 8th frame was used for films 43, 96 and 97; the time intervals are 20, 20.8 and 20.8 seconds. Every frame was used for films 29 and 141 and the respective time intervals are 11.32 and 19.7 seconds. Every second frame was used for films 37 and 38 with time intervals of 22.64 seconds. Every fourth frame was used for films 156, 147, 158 and 159; the time intervals are 20.7 seconds.

It must be borne in mind that the films give only a fragmentary record in the life of the lymphocytes. We know nothing of the age and other details about the individual lymphocytes, nor anything about their record before the period of the taking of the film except that those in the field had previously migrated there from the explant.

Some films had many more lymphocytes and migratory periods that could be plotted than others (see table 1). The length of the migratory periods also varied greatly as did the total length of the migratory time for the different films.

MIGRATION AND REST

Of the 83 migrating lymphocytes charted 45 had more than one period of migration separated by periods of rest, and 38 had no rest periods. Of the latter, 30 out of 68 in the lymph-node cultures were in the focal field from 60 to 499 seconds; out of 3 in the omentum cultures 1 was in the field 452 seconds, and out of 12 in the sarcoma cultures 7 were in the field from 207 to 828 seconds without rest periods. The source is thus of no significance in regard to the occurrence of lymphocytes without rest periods or as regards the length of the periods. It is probable that these lymphocytes migrated for some time before and after the observed period, but whether or not they had rest periods before or after is unknown. It may be that they did have rest periods, or that they were in a stage or state where migration

goes on without rest periods; or there may be two types or states of lymphocytes, one with rest periods and one without.

The 45 lymphocytes that had one or more periods of migration and rest began or ended their careers in the focal field with a migrating period that was incomplete in length, because the lymphocyte was either migrating as it entered or as it left the field or did both. The incomplete migration periods varied from a few seconds to 509 seconds in length.

TABLE 2

Migration and rest

The number of each film (No.), the number of lymphocytes used in each film (Lym.), the number of migratory periods (Per.), the minimal and maximal length in seconds of those periods (Min., Max.), the total length of the migratory time in seconds for all the lymphocytes used in each film (Mig.), the minimal and maximal length in seconds of the rest periods (Mi. Ma.), the total length of the rest time in seconds for all the lymphocytes used in each film (Rest), the average rate of locomotion in microns per minute (Rate).

NO.	LYM.	PER	MIN.	MAX.	MIG.	MI.	MA.	REST	RATE
43	48	68	30.0 to	480.0	12192.0	13	2815	5448	19.6
96	10	17	57.0 to	291.0	2772.0	10	312	1219	16.6
97	9	19	62.0 to	499.0	3317.0	21	229	1280	13.1
29	1	17	11.3 to	101.9	668.0	23	396	1607	22.4
37	2	6	45.2 to	452.0	1515.0	34	610	802	13.9
38	1	3	45.2 to	226.0	362.0	124	136	260	10.0
156	1	3	124.2 to	331.2	455.0		10	10	12.6
141	3	4	78.0 to	310.0	932.0		117	117	22.6
147	6	8	62.0 to	828.0	2874.0	60	312	372	16.4
158	1	1		207.0	207.0		0	0	22.4
159	1	2	104.0 to	124.0	228.0		88	88	16.2
	83	148			25522.0			11203	

Some of the lymphocytes that had alternate periods of migration and rest had one or more complete migration periods between rest periods. The length of these periods varied from 10 to 374 seconds for lymphocytes from lymph nodes and from 45 to 294 seconds for those from omentum, but as there were only four such migration periods for omental lymphocytes, no conclusions can be drawn as to whether there is any significant difference in the lymphocytes from the two sources. The sarcoma lymphocytes did not happen to have any interpolated migration periods.

The length of the rest periods varied as much as the migration periods. A few lymphocytes that had previously migrated into the field remained at rest during the entire time of the motion picture. Whether or not they migrated subsequently is unknown. The intermediate rest periods varied in length from 10 to 400 seconds except for one of 610 seconds and one of 1115 seconds.

Where there were several periods of migration and rest there was no special relation between the length of those periods. Relatively long or short periods of migration were followed by either long or short periods of rest, and relatively long or short periods of rest were followed by either long or short periods of migration. One might expect a long period of migration or rest to be followed by a long period of rest or migration, and a short period of migration or rest period to be followed by a short rest or migration period; this sometimes happened, but the reverse frequently occurred also.

Most of the lymphocytes were not in the field long enough to have many periods of migration and rest. One lymphocyte in film 29 was in the field 37 minutes and 55 seconds. It had 17 periods of migration and 16 periods of rest. The migration periods totalled 688 seconds and the rest periods 1607 seconds. Three other lymphocytes that were in the same field nearly as long had a considerably longer total of migration time than of rest time. The figures are as follows: lymphocyte No. 2: M 1132, R 646; No. 4: M 1370, R 995; No. 7, M 1068, R 566 seconds.

There was no special relation between the length of a rest period and the following rate of migration. The rate of locomotion after seven short rest periods, 15 to 60 seconds in length, was above the average, and after 8 it was below the average. After periods of 61 or more seconds in length, the rate after one period was above and after 5 was below the average. This would seem to indicate short periods of rest, 60 seconds or less in length, are more frequently followed by rapid locomotion than are long periods of rest, just the opposite of what one would expect. The very long resting periods (1115, 340 and 178 seconds) were followed by locomotion rates below the average.

There was no special relation between the length of a migration period and the rate of migration. During short periods (30–120 seconds) of migration, three out of 9 lymphocytes migrated at a rate

faster than the average, and during long periods (120–260 seconds) five out of 12 lymphocytes migrated at a rate faster than the average.

RATE OF LOCOMOTION

The general average rate, for all the lymphocytes measured, was 16.5 microns per minute (table 1). This includes those from lymph nodes, omentum and sarcoma measured in cultures of various ages and in several different media. The average lymphocyte, when it migrates, goes about a millimeter an hour or about an inch in 25 hours, an inch a day.

The source of the lymphocytes (table 1) has probably no special influence on the rate. The average rate of lymphocytes from lymph nodes was 17.9 and of those from sarcoma about the same—18.4 microns per minute. Those from the omentum moved more slowly—11.9 microns per minute, but as only three were measured, this difference is probably not significant.

The age of the culture did not apparently influence the rate of locomotion during the first 4 or 5 days (table 1).

The media likewise probably had no marked effect on the rate. In autoplasma the average rate was 17.9 microns, in chicken plasma 17.2, and in Gey's medium 19.3 microns per minute.

Aside from the fact that the number of lymphocytes measured was too few in chicken plasma and in Gey's medium and from omentum and sarcoma to give satisfactory averages, there are three striking features of locomotion that tend to make generalizations regarding the average rate of locomotion of uncertain value.

The three striking features of locomotion are: (1) the great variation in the rate of speed of different lymphocytes in the same culture at approximately the same time; (2) the variations of the same lymphocyte in successive periods of migration after periods of rest, and (3) the variations in the rate of the same lymphocyte from moment to moment.

(1) The average rates of speed for the 68 migration periods of the 48 lymphocytes in film 43 varied from 9.6 to 35.1 microns per minute. In other words, some lymphocytes in the same field at the same time moved almost four times as fast as others. The lymphocytes in the other films also showed variations. In film 96 the rates varied from

11.7 to 23.4, in 97 from 10.2 to 16.3, in 37 from 9.7 to 26.2, in 38 from 9.6 to 10.5, in 156 from 11.9 to 13.4, in 141 from 13.4 to 31.2, in 147 from 10.9 to 24.9 and in 159 from 13.5 to 19.0 microns per minute.

(2) The variations of the rate of locomotion in the same lymphocyte is well illustrated by the lymphocyte from film 29 which had 17 separate periods of migration. The rates for the different periods varied from 9.2 to 42.9 microns per minute. The average rates for the successive 17 periods were as follows: 16.5, 16.5, 21.5, 22.8, 17.5, 9.2, 20.2, 27.5, 20.9, 19.0, 20.3, 28.3, 24.2, 42.9, 30.6, 25.8 and 18.2 microns per minute. Sometimes the average rates for successive migratory periods were fairly uniform, where only three or four periods were recorded.

(3) The variations in speed of the same lymphocyte from moment to moment were about as marked as the variations of the same lymphocytes from period to period or of different lymphocytes in the same culture. For example, lymphocyte No. 39 from film 43 moved for successive 20-second intervals at the following rates per minute in microns: 13.5, 30.3, 18.3, 19.4, 28.2, 27.3, 3.0, 16.2, 19.4, 16.2, 23.1, 28.2, 6.6, 19.4, 23.4.

SUMMARY

The locomotion of 84 lymphocytes having 148 periods of migration covering 25522 seconds or about 8 hours was determined from motion pictures made of the lymphocytes in cultures of tissues from several sources in several different media. Forty-five of the 83 migrating lymphocytes had more than one period of migration separated by rest periods. There was no regularity in the length of these periods. Those from lymph nodes and Walker sarcoma 338 had about the same general rate of locomotion and the same variations in rate. Those from the omentum were slowed but the number of lymphocytes studied was probably too few to be significant. Average rates for lymphocytes in lymph nodes cultures varied from 13.1 to 22.4 microns per minute, in omentum cultures, from 10.0 to 13.9 microns per minute, and in sarcoma 338 cultures, from 12.6 to 22.6 microns per minute. The general average for all lymphocytes was 16.5 microns per minute. The source of the lymphocytes, the age of the culture, and the nature of the medium had no important effect on the rate. One feature was

the variation in the average rates of different lymphocytes in the same culture at the same time, as in film 43 where the speed varied from 9.6 to 35.1 microns per minute. That is, lymphocytes from the same source in the same environment at the same time move at greatly different rates. A second feature was the variation in the rate of the same lymphocyte from period to period. A third feature was the variation in speed from moment to moment. The most rapid rate of speed for a short interval of 20 seconds was 55.5 microns per minute.

LITERATURE

BUNTING, C. H., AND J. HUSTON 1921 Fate of the lymphocyte. *J. Exper. Med.*, **33**, 593.

LEWIS, W. H. 1931 On the locomotion of lymphocytes. *Anat. Rec.*, **48**, *Suppl.* 52.

Idem 1931a Locomotion of lymphocytes. *Johns Hopkins Hosp. Bull.*, **49**, 29–36.

Idem 1932 The locomotion rate of rat lymphocytes in plasma cultures. *Anat. Rec.*, **52**, *Suppl.* 65.

LEWIS, W. H., AND L. T. WEBSTER 1921 Migration of lymphocytes in plasma cultures of human lymph nodes. *J. Exp. Med.*, **33**, 261–269.

MAST, S. O. 1926 Structure, movement, locomotion and stimulation in amoeba. *J. Morph. and Physiol.*, **41**, 347–425.

MCCUTCHEON, M. 1924 Studies on the locomotion of leucocytes. III. The rate of locomotion of human lymphocytes *in vitro*. *Amer. J. Phys.*, **69**, 280–282.

MURPHY, J. B., AND A. W. M. ELLIS 1914 Experiments on the rate of lymphoid tissue in the resistance to experimental tuberculosis in mice. *J. Exper. Med.*, **20**, 397–403.

MURPHY, J. B., AND H. D. TAYLOR 1919 The lymphocyte in natural and induced resistance to transplanted cancer. *Ibid.*, **28**, 1–9.

TAYLOR, H. D., AND J. B. MURPHY 1917 Experiments on the rôle of lymphoid tissue in the resistance to experimental tuberculosis in mice. II. Effect of cancer immunity on resistance to tuberculosis. *Ibid.*, **25**, 609–617.

WISEMAN, B. K. 1931 The induction of lymphocytosis and lymphatic hyperplasia by means of parenterally administered protein. *Ibid.*, **53**, 499–510.

WISEMAN, B. K. 1931 Criteria of the age of lymphocytes in the peripheral blood. *Ibid.*, **54**, 271–294.

WISEMAN, B. K. 1932 The identity of the lymphocyte. *Folia Haematologica*, **46**, 346–358.

BOOK REVIEWS

Lang's German-English Dictionary of Terms Used in Medicine and The Allied Sciences with Their Pronunciation. Revised and edited by MILTON K. MEYERS. 4th Edition, enlarged. 926 pp. (*P. Blakiston Sons & Co., Inc., Phila., 1932.*)

This valuable handbook, indispensable to all medical librarians and research workers, derives from the earlier vocabularies of G. R. Cutter [1879], Fancourt Barnes [1882], Treves and Lang [1890]. The fourth edition comprises 56,500 definitions, of which 3,500 are new, with the superadded feature of an English pronunciation for each term.

F. H. G.

A Standard Classified Nomenclature of Disease. Compiled by the National Conference on Nomenclature of Disease. Edited by H. B. LOGIE. 702 pp. $3.50. (*The Commonwealth Fund, N. Y., 1933.*)

The merits of this classification were discussed at a dinner given by Dr. Welch during the current year. The arrangement is minute and exhaustive, designed to cover any problem in diagnosis which may come up in hospital or dead-house. It is supplemented by lists of non-diagnostic terms relating to semeiology and obstetric conditions, unclassifiable terms and a most useful subject-index. The fundamentum divisionis is (1) The site of the disease (tissue or organ); (2) The presumable cause, *viz.*, prenatal influences, microorganisms, intoxication, trauma or physical agents, circulatory or neuropsychic disturbances, abnormity, disorders of metabolism, growth, or nutrition, neoplasms, unknown or uncertain causes. The place in the total scheme is indicated by code numbers allocated to the site and to the cause, if ascertainable, and can be obtained, in each case, from the terminal index. The success of the venture will turn upon its ultimate practical utility in the hospitals which have adopted it.

F. H. G.